Impact of Fungal Infection on the Continuity of Chemotherapy and Disease Outcome during Induction and Consolidation Therapy of Childhood Acute Lymphoblastic Leukemia

Thesis

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بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ تَكُنْ
تَعْلَمُ وَكَانَ فَضْلُ
اللهِ عَلَيْكَ عَظِيمًا
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List of Abbreviations

Abb.	Full term
ANC	Absolute Neutrophil Count
ALL	Acute Lymphoblastic Leukemia
ARDS	Acute Respiratory Distress Syndrom
BMA	Bone Marrow Aspirate
CDC	Centers for Disease Control and Prevention
CLABSI	Central Line Associated Blood Stream Infection
CNS	Central Nervous System
CVC	Central Venous Catheter
CSF	Cerebrospinal Fluid
CML	Chronic Myeloid leukemia
CR	Complete Remission
CMV	Cytomegalo Virus
DTP	Differential time to positivity of blood cultures
ESBL	Extended Spectrum Beta Lactamase
HSCT	Haematopoeitic stem cell transplantation
HCW	Health Care Worker
HSV	Herpes Simplex Virus
HEPA	High Efficiency Particulate Air
IPT	Immunophynotyping
IFD	Invasive Fungal disease
IFI	Invasive Fungal Infection
MARSA	Methicilin aminoglycoside resistant staphylococcus aureus
MRD	Minimal Residual Disease
NCCN	National Comprehensive Cancer Network
PAC	Primary Antifungal Chemoprophylaxis
TXV	Total fifteen
VRE	Vancomycin resistant enterococci
VZV	Vareicella Zoster Virus

INTRODUCTION

Invasive fungal infections (IFIs) pose a serious threat to patients with acute leukemia undergoing chemotherapy or stem cell transplantation (SCT). They are difficult to diagnose due to nonspecific clinical manifestations and trouble with obtaining appropriate material to document infection, especially in sick children resulting in high mortality rates.

Autopsy studies revealed fungal infections in 25–31% of patients with leukemia with the incidence varying considerably among countries. Few data are available on the epidemiology and clinical characteristics of IFI in children with leukemia. The incidence rate varies between 4.9% and 29% in leukemic children not receiving antifungal prophylaxis (AFP) and between 2% and 4% in those given systemic AFP during intensive chemotherapy ***(Kaya et al., 2009).***

Clinical and laboratory diagnosis of these infections are neither sensitive nor specific and are generally limited in detection of invasive fungal infections. Culture detection of fungal species is often delayed because of slow or absent growth of fungal isolates from clinical specimens ***(Richardson et al., 2000).***

High-resolution CT scan pictures showing a halo sign or crescent air sign are helpful for establishing the diagnosis of invasive aspergillosis. Sandwitch ELISA can be used to detect circulating galactomannan in serial serum samples, PCR of blood samples may also be used ***(De Mari, 2000).***

Modified European Organisation for the Research and Treatment of Cancer (EORTC)/Mycosis Study Group (MSG), **EORTC / MSG** criteria classified patients in the category **probable IFD** as soon as they presented with host criteria and at least one major clinical criterion or two minor clinical criteria, i.e. the presentation of ongoing fever in neutropenia and typical radiographic findings in high-resolution computerised tomography sufficed to reach the upgraded category. To reach the category proven, patients were obliged to have microbiological or histopathological proof of fungal disease ***(Christina et al., 2010).***

Antifungal therapy had been quite limited in the past. The gold standard of therapy has been amphotericin B, a polyene antifungal agent with considerable toxicity. Voriconazole, has been shown to be more effective than amphotericin B as first-line therapy of invasive aspergillosis, in a randomized trial ***(Wingard et al., 2005).***

New antifungal agents have been introduced into the clinical area and more are arriving. Caspofungin, a member of a unique class of agents, the echinocandins, was licensed several years ago. With excellent activity against the two most frequent invasive fungal pathogens, Candida and Aspergillus, and an outstanding safety profile, caspofungin has rapidly become widely used.

Even with effective and safe therapeutics, treatment is frequently started late during the course of infection, when the burden of organisms is high and the likelihood of therapeutic success is low. This accounts for much of the extraordinarily high mortality. Accordingly, considerable attention has been paid to different antifungal strategies ***(Wingard et al., 2005).***

AIM OF THE WORK

- Monitoring the effect of fungal infection on disease treatment regarding (delays for chemotherapy) and disease outcome (remission state) during the induction and consolidation therapy.
- To assess the response to the different antifungal agents and outcome of fungal infections during induction and consolidation period.

ACUTE LYMPHOBLASTIC LEUKEMIA

Definition of acute lymphocytic leukemia

Acute lymphocytic leukemia (ALL), also called acute lymphoblastic leukemia, is a cancer that starts from white blood cells called lymphocytes in the bone marrow (the soft inner part of the bones, where new blood cells are made). Leukemia cells usually invade the blood fairly quickly. They can then spread to other parts of the body, including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles (in males). Other types of cancer also can start in these organs and then spread to the bone marrow, but these cancers are not leukemia. The term "acute" means that the leukemia can progress quickly, and if not treated, would probably be fatal within a few months. Lymphocytic means it develops from early (immature) forms of lymphocytes, a type of white blood cell ***(American Cancer Society, 2013).***

Signs and symptoms

Acute lymphocytic leukemia (ALL) can cause many different signs and symptoms. Most of these occur in all kinds of ALL, but some are more common with certain subtypes. General symptoms, Patients with ALL often have several non-specific symptoms. These can include: Weight loss, Fever, Night sweats, Fatigue, Loss of appetite, recurrent infections, bleeding, such as frequent or severe nose bleeds and bleeding gums.

Swelling in the abdomen, Leukemia cells may build up in the liver and spleen, causing them to enlarge. This might be noticed as a fullness or swelling of the belly or feeling full after eating only a small amount. The lower ribs usually cover these organs, but when they are enlarged the doctor can feel them.

Enlarged lymph nodes of the neck, in the groin, or in underarm areas), might be noticed as lumps under the skin. Lymph nodes inside the chest or abdomen can be detected only by imaging tests such as CT or MRI scans.

Bone or joint pain, sometimes leukemia cells build up near the surface of the bone or inside the joint and cause bone or joint pain.

Spread to other organs. Less often, ALL spreads to other organs and forms tumors, If ALL spreads to the brain and spinal cord it can cause headaches, weakness, seizures, vomiting, trouble with balance, facial numbness, or blurred vision. Rarely, ALL may spread to the skin, eyes, testicles, kidneys, or other organs ***(American Cancer Society, 2013).***

Diagnosis of acute lymphoblastic leukemia

Blood test:

May reveal too many white blood cells, not enough red blood cells and not enough platelets. A blood test may also show the presence of blast cells immature cells normally found in the bone marrow but not circulating in the blood.

Bone marrow tests:

Routine exams under a microscope:

A diagnosis of ALL generally requires that at least 20% of the cells in the bone marrow are blasts.

Flow cytometry and immunohistochemistry:

These tests are used for *immunophenotyping*.

Cytogenetics:

Most of the chromosome changes in adult ALL are translocations. The most common one is a translocation between chromosomes 9 and 22 [often written t (9; 22)], which results in a shortened chromosome 22 (called the *Philadelphia chromosome*). About 1 out of 4 adults with ALL have this abnormality in their leukemia cells.

Fluorescent in situ hybridization (FISH):

This is another type of chromosome test.

Lumbar puncture (spinal tap)

This test looks for leukemia cells in the cerebrospinal fluid (CSF).

Imaging tests:

X-rays, Computed tomography (CT) scan, Magnetic resonance imaging (MRI) scan, Ultrasound ***(American Cancer Society, 2013).***

Treatment

Treatment options for each patient are based on the leukemia subtype as well as certain prognostic features. The main types of treatment used for ALL are: Chemotherapy, Targeted therapy, Stem cell transplant other treatments such as surgery and radiation therapy may be used in special circumstances.

Chemotherapy for acute lymphocytic leukemia

Chemotherapy (chemo) is the use of drugs to treat cancer. Most often, these drugs are injected into a vein, into a muscle, under the skin, or taken by mouth. The drugs travel through the bloodstream to reach cancer cells all over the body. This makes chemo useful for cancers such as leukemia that has spread throughout the body. Most chemo doesn't reach the area around the brain and spinal cord well, so it may need to be injected into the Cerebrospinal fluid to kill cancer cells in that area. This is called *intrathecal chemo*. Doctors give chemo in cycles, with each period of treatment followed by a rest period to allow the body time to recover. Because of its potential side effects, chemo is sometimes not recommended for patients in poor health, but older age by itself should not stop someone from getting chemo if they need it and are healthy. Chemo for acute lymphocytic leukemia (ALL) uses a combination of anti-cancer drugs. They are given in 3 phases, induction and consolidation and maintenance phases usually over the course of about 3 years The most commonly used drugs include: